SYVÄAIVOSTIMULAATION TOTEUTTAMINEN VAIKEAHOITOISESSA EPILEPSIASSA

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Epilepsia on vakava neurologinen sairaus, josta kärsii noin prosentti väestöstä. Epilepsian ensisijainen hoitomuoto on epileptisiä kohtauksia hillitsevä lääkitys – joko monoterapiana tai useamman lääkkeen yhdistelmähoitona. Kuitenkin jopa kolmasosa potilaista on lääkkeille huonosti reagoivia, eikä kaikkien potilaiden kohtaustilannetta saada hallintaan edes leikkaushoidolla tai vagushermostimulaatiolla (vagus nerve stimulation, VNS).

Syväaivostimulaatio (deep brain stimulation, DBS) on neurostimulaation muoto, jossa sähkövirtaa syötetään aivojen syviin rakenteisiin – yleisimmin tyvitumakkeisiin. Syväaivostimulaatiota käytetään hoitomuotona moniin erilaisiin neurologisiin häiriöihin, kuten liikehäiriöt, mielenterveyden häiriöt ja epilepsia. Epilepsiassa yleisin ja lupaavin stimulaatiokohde on tällä hetkellä talamuksen anteriorinen tumake (anterior nucleus of thalamus, ANT). ANT-DBS on Euroopassa hyväksytty lääkkeille reagoimattoman epilepsian hoitoon vuonna 2010. Perusteena hyväksymiselle oli samana vuonna julkaistu Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy -tutkimus (SANTE).

SANTE-tutkimuksessa raportoitiin yksittäisestä potilaasta, jolle ANT-DBS aiheutti suuren määrän uudentyyppisiä kohtauksia, jotka erosivat selkeästi potilaalle tyypillisistä kohtauksista. Stimulaatiossa käytettävien parametrien muuttamisen jälkeen näitä kohtauksia ei enää esiintynyt, eikä parametrien palauttaminen alkuperäisiin arvoihin myöhemmin enää aiheuttanut uusia kohtauksia. TAYS:ssa on 2011 todettu ANT-DBS -potilaan videoelektroenkefalografiatutkimuksessa (vEEG) vastaavia potilaalle epätyypillisiä kohtauksia, jotka myös ”katosivat” stimulaatioparametrien muutoksen jälkeen.

Tampereella hoidetun potilaan tapauksessa havaittiin epätyypillisten kohtausten lisäksi näköaistin oireita. Sekä kohtaukset että näköoireet olivat vEEG:n perusteella selkeästi yhteydessä DBS-hoitoon. Molemmat kuitenkin loppuivat stimulaatiojännitteen laskemisen jälkeen, eikä jännitteen palauttaminen alkuperäiselle tasolle tuonut oireita takaisin. Pidempiaikaisessa seurannassa potilas sen sijaan hyötyi selkeästi DBS-hoidosta: Sekä kohtausten määrä että vakavuus väheni merkittävästi. Tämän perusteella esitämmekin hypoteesin siitä, että ANT-DBS -hoidon alkuvaiheessa esiintyvät lyhytaikaiset, poikkeukselliset kohtaukset ym. oireet saattavat ennakoida myöhempää positiivista vastetta hoidolle.

Tämän opinnäytteen alkuperäisyys on tarkastettu Turnitin OriginalityCheck-ohjelmalla Tampereen yliopiston laatujärjestelmän mukaisesti.

Stimulation induced electrographic seizures in deep brain stimulation therapy of the anterior nucleus of the thalamus predict a favorable treatment response

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Abstract

Deep brain stimulation (DBS) is a method of neuromodulation used in the treatment of several movement disorders, psychiatric disorders and epilepsy. In the field of treatment of refractory epilepsy, anterior nucleus of the thalamus (ANT) has proven to be the most promising stimulation target. A major challenge with DBS as a treatment method is the uncertainty concerning treatment outcome. Better ability to predict favorable treatment outcomes would ease the selection of patients as well as reduce the amount of treatment-related adverse effects. We present a case of a single patient suffering from drug-resistant epilepsy who received ANT-DBS therapy at the Tampere University Hospital. This particular patient underwent a long-term video electroencephalography (vEEG) recording during which the response to ANT stimulation was monitored. The initial response was the appearance of a completely new type of a visual symptom along with atypical seizures differing from the seizure type previously diagnosed for this patient – simultaneously with the onset of DBS. Lowering the stimulation voltage alleviated these symptoms. However, returning the voltage to the initial value did not cause the recurrence of either the visual symptoms or the new seizure type. On the contrary, the same stimulation parameters causing the initial adverse effects appeared to alleviate the patient's seizures in long-term follow-up. We therefore hypothesize that the occurrence of stimulation induced seizures at the onset of DBS therapy could predict a later favorable response to the treatment.

1 Background

Epilepsy is a significant neurologic disorder which can greatly affect a patient's quality of life. Epilepsy has a prevalence of up to 1,0 % (1), and approximately one third of patients with epilepsy do not gain sufficient benefit from treatment with antiepileptic drugs (AEDs) (2). Even though some of these cases can be treated with resective surgery or vagal nerve stimulation (VNS), adequate seizure control is still not achieved in all patients. This group of patients must be considered as possible candidates for deep brain stimulation (DBS) therapy. DBS is a method of neuromodulation with the aim to modulate the activity of epileptic brain networks in a way that suppresses epileptic seizures. Although its exact mechanisms remain to be completely understood, DBS has achieved positive treatment results in both animal and human studies (2–16).

The most widely known study in the field of DBS for epilepsy is the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial, a multicenter double-blinded randomized controlled trial, in which a group of 110 patients received deep brain stimulation of the anterior nucleus of the thalamus (ANT) (5). In the blinded phase, patients were divided into control and stimulation groups, and only the stimulation group received DBS. After the blinded phase, both groups received stimulation. The SANTE study group reported of two patients who experienced "acute, transient stimulation-associated seizures". One of these patients is more widely known as the "outlier patient". This patient experienced a remarkable amount of atypical seizures due to ANT stimulation and the onset of these seizures was evidently related to the stimulation. This patient was labeled as an outlier and eliminated from the statistical analysis. What makes the outlier patient intriguing is the fact that the same stimulation parameters initially causing these atypical seizures later led to a decrease in the patient's seizure frequency.

We report a case of a patient resembling the outlier of the SANTE trial. During video electroencephalography (vEEG) recording, our patient responded to ANT-DBS therapy with similar occurrence of a new type of seizure as well as distinct visual symptoms. Equally in the current case, the initial unfavorable response evolved into a beneficial treatment outcome for the patient. In the limits of our knowledge, there are no published reports of similar cases.

2 Case presentation

We present a case of a 30-year-old (at the time of vEEG-monitoring in 2011) male patient. Our patient was diagnosed with temporal lobe epilepsy with brief complex partial seizures (focal unaware, as defined by ILAE 2017 classification of seizure types (17)) at the age of 11, with some seizures propagating to secondarily generalized tonic-clonic seizures (focal to bilateral tonic-clonic, ILAE 2017 (17)). A specific characteristic for the seizures of this patient was the usual occurrence of tonic-clonic seizures associated to waking up in the morning. He also has a history of several episodes of status epilepticus (SE), leading to hospitalization. Seizures were initially defined to be of temporal origin due to early EEG-findings. However, in the context of comprehensive epilepsy surgery evaluation, conducted in 2005, the etiology of epilepsy was found to be bilateral occipital cortical dysplasia. Consequently, epileptogenic zone was determined to be located in the occipital lobe and temporal lobe was defined as the ictal onset zone. The patient underwent most of the available AED-therapies with multiple combinations of different anticonvulsants and received VNS from 2005 until 2010, which all failed to adequately suppress his seizures. Due to the etiology of cortical dysplasia, our patient was not a candidate for resective surgery either. These circumstances led to consideration of installing DBS-device for our patient, and in November 2010, DBS electrodes

(model 3389, Medtronic, Minneapolis, MN, USA) and an internal pulse generator (Activa PC, Medtronic, Minneapolis, MN, USA) were successfully implanted.

The patient's mean seizure frequency during the five-month baseline period was 12.2 seizures per month, 60 of the 61 seizures being tonic-clonic. Early treatment with ANT-DBS resulted in minor – but temporary – decrease in the seizure frequency, possibly due to microlesion effect described in certain studies (3, 10). Original stimulation parameters immediately after the surgery were set to 5 volts amplitude, 90 µs pulse width, 140 Hz frequency and 1 min ON 5 min OFF cycle. Contacts labeled 2 and 10 were initially active (Figure 1). Voltage was gradually increased to 7 volts. As the effect of microlesion began to recede and the patient's seizures returned to baseline values, active contacts were switched to contacts 1 and 9 (Figure 1). Again, voltage was first set to 5 volts and then increased to 7 volts. Other parameters were maintained at their original values. Occurrence of a status epilepticus episode shortly after this adjustment indicated that these stimulation parameters were not optimal, and the stimulator was shut down for the time being.

In April 2011, the patient was called in for a three-day vEEG-monitoring to determine the optimal stimulation parameters in a controlled setting. At the time, his daily medication was set to 1200 mg of carbamazepine and 30 mg of clobazam. DBS device was switched on during the second day, and stimulation parameters were set to 5 volts, 90µs, 180 Hz and 1 min ON 5 min OFF – with contacts 3 and 11 being active (Figure 1). Shortly after, at the onset of stimulator ON phase, the patient reports a transient visual symptom consisting of "fogginess" of vision, especially at the periphery of his visual field. The patient reports this symptom simultaneously with the onset of ANT stimulation without any abnormalities in the EEG pattern, as is illustrated in the EEG graph (Figure 2). Later the same day, as the patient is having a conversation with his roommate, the onset of stimulator ON phase simultaneously provokes seizure activity clearly seen in the EEG (Figure 3). Clinical manifestations of this seizure differ from the patient's habitual seizures: The patient is seemingly able to continue the conversation, but when the nurse enters the room and starts interviewing the patient, he complains that colors seem different than normally and that the text on a magazine "rises upwards from the paper". After the settling of the seizure, the patient claims to have no memory of his discussion with the nurse. During the third day, the patient reports multiple visual symptoms including black to barely visible spheres traveling through his field of vision and bright stripes with dots appearing and disappearing.

All of these symptoms vanish as the stimulation voltage is decreased to 3 volts during the third day of the recording. The voltage is later that day returned to the value of 5 volts and in long-term stimulation was increased up to 7 volts without the recurrence of these symptoms or seizures. On the contrary, our patient had long seizure free periods and his overall seizure frequency decreased significantly: During the last five months of a 40-month follow-up, our patient had a mean of 1.6 seizures per month. In addition, most of our patient's seizures during later ANT-DBS therapy were his habitual focal unaware seizures instead of tonic-clonic seizures, which indicates that DBS prevented seizure propagation and reduced seizure severity (Figure 4).

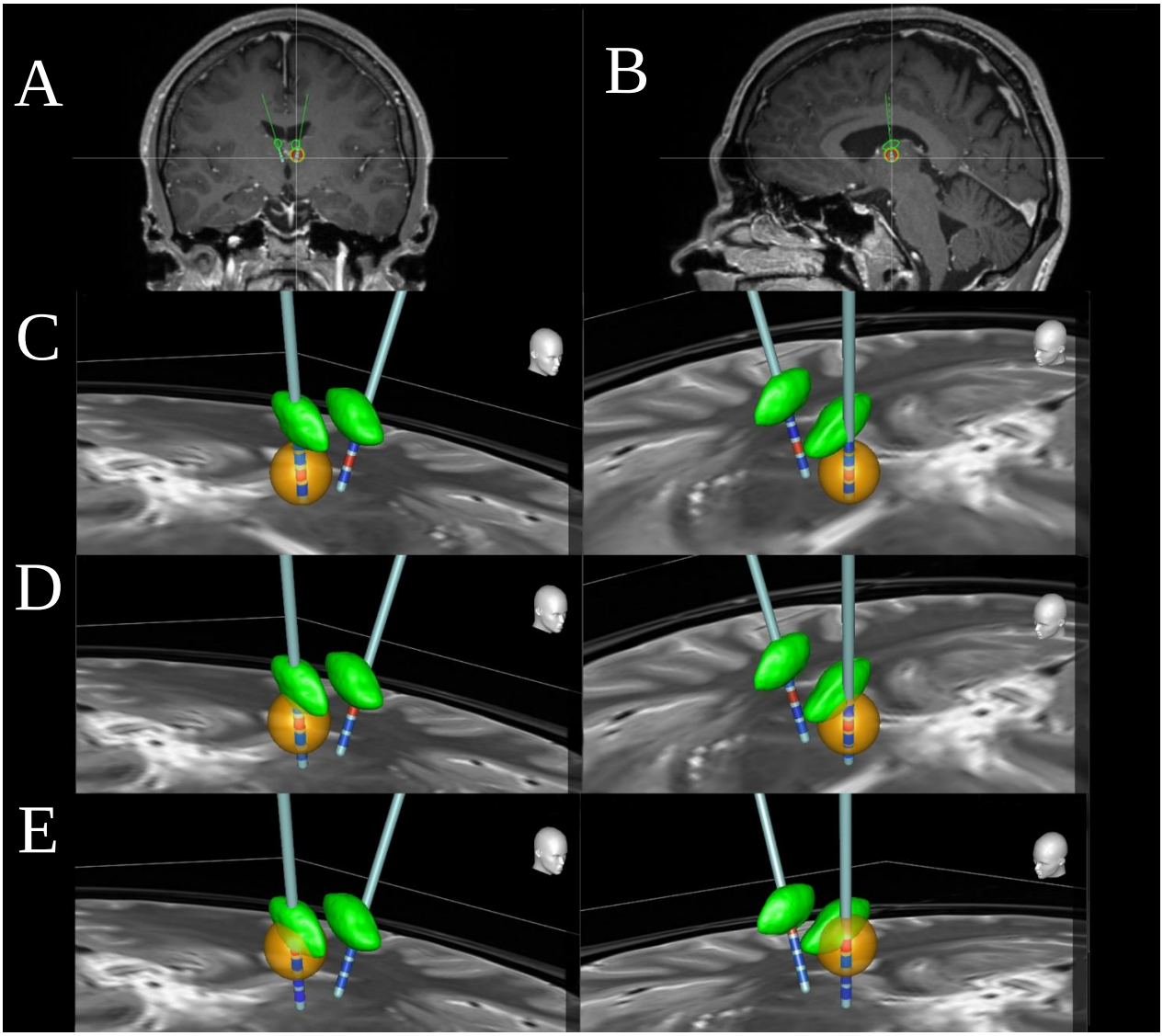

Figure 1. The locations of the DBS leads in coronal (A) and sagittal (B) slices. Panels C, D and E illustrate the estimated distribution of the electrical field (orange) generated by different active contacts (red) in both right and left ANT (green). Inactive contacts are represented with blue color. Images were generated using the SureTune software (Medtronic, Minneapolis, MN, USA). From bottom to top, contacts are labeled as 0, 1, 2 and 3 on the left side and as 8, 9, 10 and 11 on the right side. (C) Contacts 1 and 9 are active. The electrical field completely misses the ANT. (D) Contacts 2 and 10 are active. The electrical field still barely reaches the ANT. (E) Contacts 3 and 11 are active. The electrical field extends to the inferior section of ANT. Clinical effect was achieved only with this setting.

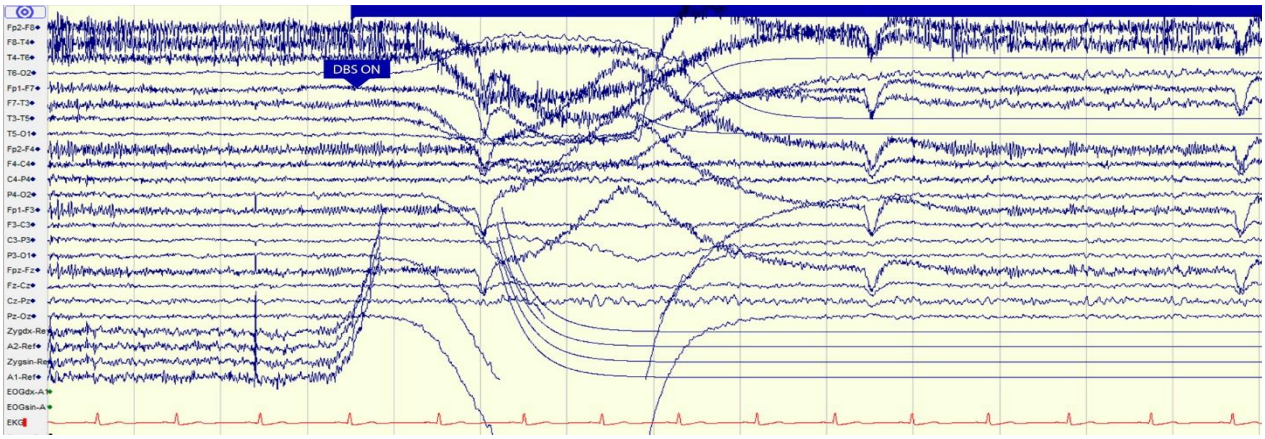

Figure 2. The onset of a DBS ON period (blue arrow) shown in an EEG graph. The patient reported the visual symptom immediately after the onset of stimulation, but the EEG pattern remains normal. The sharp "drop" seen in the graph in some channels is an artifact caused by the monopolar cathodal stimulation.

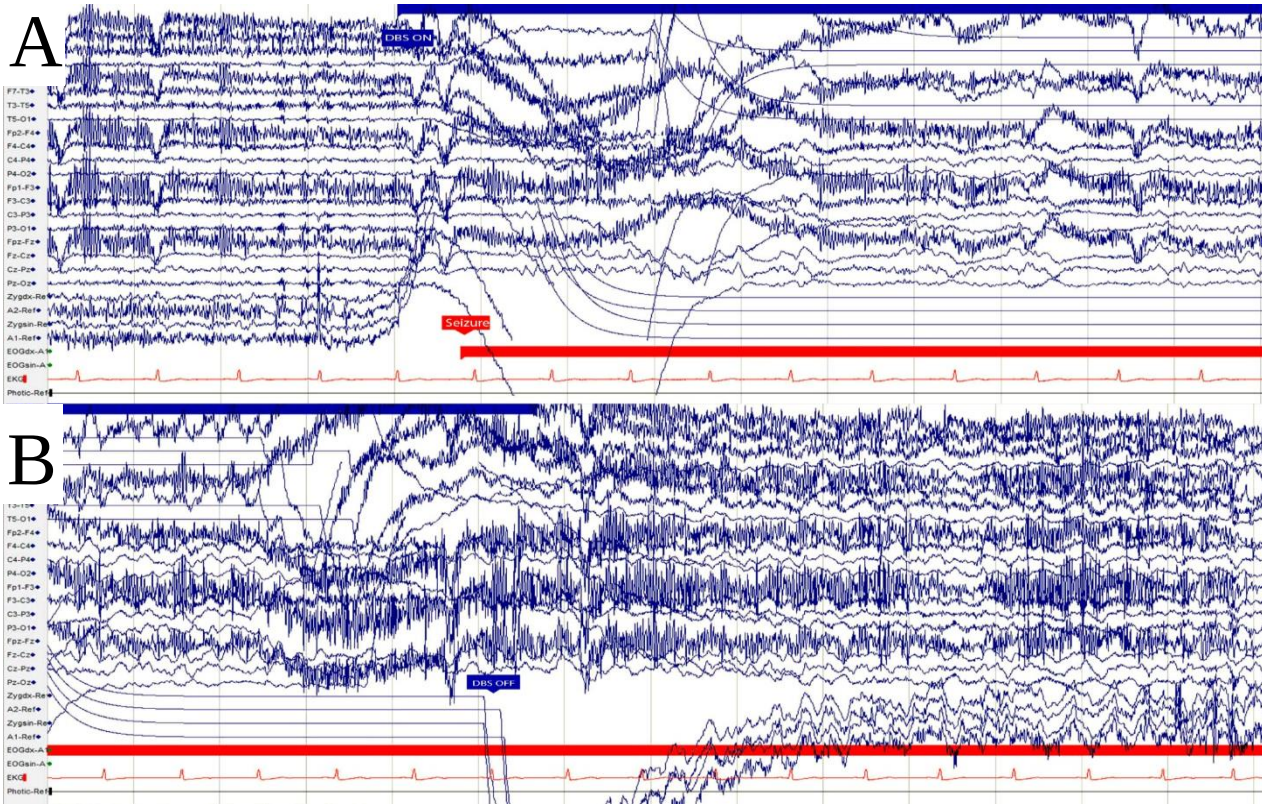

Figure 3. (A) The onset of a DBS ON period (blue arrow) and the onset of an epileptic seizure (red arrow) shown in an EEG graph. (B) EEG graph illustrating how the ictal activity continues even after the end of DBS ON period (blue arrow). The sharp "drop" seen in the graph in some channels is an artifact caused by the monopolar cathodal stimulation.

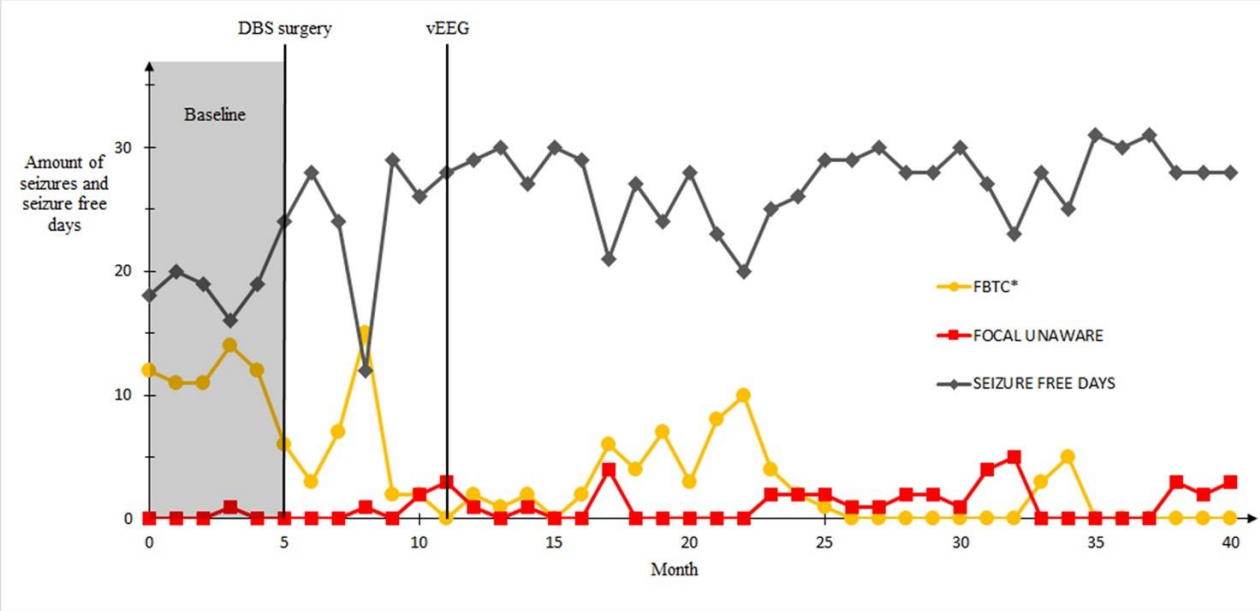

Figure 4. Seizure frequencies and the amount of seizure free days before and after the DBS surgery in a follow-up of 40 months. First five months represent the baseline seizure frequency (gray area), DBS-surgery was conducted on month five. The vEEG-recording was conducted on month 11. Seizures that occurred during the vEEG not included. Seizure classification according to ILAE 2017 guidelines. *Focal to bilateral tonic-clonic

3 Discussion

The occurrence of atypical seizures provoked by DBS was also noted in the SANTE trial in form of the outlier patient, as mentioned above. Further details concerning the new seizures the outlier patient experienced are provided in a dataset (18) with which the manufacturer of DBS electrodes, Medtronic, applied for Food and Drug Administration's (FDA) approval of ANT-DBS in the United States. Onset of these seizures was simultaneous with the onset of DBS, and they differed from the patient's habitual seizures in seizure duration and postictal period – both being significantly shorter. The seizure type, complex partial seizure (focal unaware, ILAE 2017 (17)) remained essentially the same. At the time of onset of DBS therapy and the occurrence of atypical seizures, the stimulation parameters were set to 5 volts, 90 µs and 145 Hz. During a time period of 48 hours the outlier patient experienced 210 of these brief seizures, after which the stimulation amplitude was reduced to 4 volts resulting in the cessation of these seizures. After seven months, the stimulation parameters were restored to their original values and after month 13, voltage was increased up to 9 volts. However, no recurrence of the atypical seizure type could be witnessed.

The selection of stimulation parameters for each patient is a critical point in the commencement of DBS therapy. Generally in DBS therapy, adjustments of the parameters produce a U-shaped response (19). This concept is explained by the observed change in symptom severity for better or worse as voltage, frequency or pulse width is increased from a subtherapeutic value. Gradual increase typically results in desired symptom alleviation. Increasing the parameters beyond this optimal point may, however, exacerbate the original symptoms or cause adverse effects. The location of electrodes in relation to the ANT is another important factor. Subtle variations in the location of the nucleus and differences in electrode locations even within the ANT can greatly affect treatment outcome (20). This also highlights the significance of proper selection of active contacts, even when the electrode

placement is accurate. Clinical benefit is rarely achieved with contacts outside of or in the posterior region of ANT, likely due to the insulating effect of the white matter lamina surrounding the ANT and the more extensive connections of anterior region of the ANT (20). Findings in our patient are consistent with this knowledge, as can be seen in Figure 1. Only the topmost contacts – labeled 3 and 11 – activate a sufficient number of neurons in the anterior ANT to achieve seizure suppression (Figure 1E).

In the current case, we conclude that the selected parameters and contacts must be close to optimal, since they eventually lead to a decrease in seizure frequency and severity. However, the initial appearance of visual symptoms and new seizures is inconsistent with this conclusion. The U-shaped response of our patient appears to have shifted for an unknown reason. This shift also occurs during a very brief time period of just some hours, in contrast to the SANTE outlier whose initial response remained the same for a couple of days. The SANTE study group restored the stimulation voltage to the original value only after seven months, whereas in the current case this was done the same day. The outlier patient received stimulation at 4 volts long enough for plasticity of the brain to possibly play a major role in the altered treatment response. Our patient's brain couldn't have undergone such anatomical changes in the short time window he received stimulation at lower voltage – meaning there has to be some other mechanism.

Suggested mechanisms of DBS include short, medium and long-term effects (21, 22). Both inhibition and excitation are thought to be responsible for these effects. Due to the limited time frame during which our patient's response to DBS changed, we assume that long term effects – such as synapse plasticity – have little to no significance in this case. Medium-term effects include alterations in the levels of neurotransmitter, such as GABA and glutamate. The possible role of alternating neurotransmitter levels in the current case is unclear and cannot be adequately assessed from the patient data available. Another proposed mechanism is the rapid disruption of pathologic oscillations by "jamming" them with DBS pulses (19, 21, 22). The systems oscillator theory offers a deeper insight into different physiologic and pathologic oscillations in brain networks (19). The basis of this theory is the existence of numerous groups of neurons, termed nodes, that act as oscillators across different networks. The nodes and oscillatory systems have their own frequencies, and their combined activity enables complex brain functions. Neurologic disorders are the result of flaws in the activity of these oscillators, which lead to corruption of the information carried by neural networks. DBS at right parameters – frequency being the key one in this case – may achieve clinical benefits by resonating with these oscillations and correcting or amplifying the generated information. It may also simply overrun the pathologic oscillations and therefore prevent the propagation of misinformation that is suggested to be the cause of some symptoms. In the current case, the changes witnessed in stimulation outcome might be the result of DBS alternating the oscillations in a complex way that yields positive results only after a set period of time.

We must also take into consideration the occipital cortical dysplasia our patient suffers from. The anatomical anomalies in the brain networks may cause various complex changes in the oscillations generated in that area. However, the fact that the patient ultimately became a responder and benefitted from the stimulation remains. The vEEG data and the EEG graph provided in Figure 3 also demonstrate how the atypical symptoms and seizures were induced by the stimulation of ANT. Considering that the same parameters both provoked these transient effects and later alleviated the patient's habitual seizures, we conclude that the occurrence of seizures provoked by DBS therapy could act as a biomarker for favorable treatment outcome. At the very least, initial effects caused by stimulation should not be regarded outright negative, as they might be a part of the process in which DBS modifies brain networks.

In this report, we have raised the question of how deep brain stimulation can provoke seizures with parameters later leading to favorable treatment outcome. We have also reflected on the possible mechanisms responsible for these events, as well as on the possibility of considering findings similar to the ones described here and on the SANTE materials as clinical biomarkers in ANT-DBS therapy. The discovery of an unambiguous biomarker for favorable clinical response to ANT-DBS would greatly aid patient selection for operation. This would also reduce the amount both surgery and stimulation related adverse effects. Future research should emphasize this objective, whether by the means of electrophysiological methods or different imaging techniques. Further research is also needed to more generally assess how the effects of DBS on the electrical activity of the brain are represented in different modalities used in neurologic research.

4 Concluding remarks

Deep brain stimulation has successfully been used to treat multiple neurologic disorders, including epilepsy. Of the many challenges DBS faces as a treatment method for intractable epilepsy, the inability to reliably predict the treatment outcome is a major one. This case report offers an insight into a possible solution to this problem using electroencephalography findings as possible biomarkers. Our hypothesis is that stimulation induced electrographic seizures could be considered as a potential indicator of future favorable treatment outcome.

5 Conflict of interest

KL and JP have received speaker and consultation fees from Medtronic.

6 Author contributions

TN contributed significantly to the collection of patient information, conception and design of the study, and drafted the manuscript. HH and MT contributed to the collection of EEG data and assisted in interpreting it. KL and JP critically revised the earliest version of the manuscript and assisted in improving it with their expertise. KL provided us with the Suretune materials. All the authors revised the draft and gave their approval of the version to be published.

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